Corneal Fluorescein Staining Correlates with Visual Function in Dry Eye Patients

Minako Kaido, Yukibiro Matsumoto, Yuta Shigeno, Reiko Ishida, Murat Dogru, and Kazuo Tsubota

PURPOSE. To investigate the changes in functional visual acuity (VA) and higher order aberrations in dry eye patients.

METHODS. In this prospective comparative case series, 22 right eyes were classified into those with or without superficial punctate keratopathy (SPK) in the central cornea of 22 patients with Sjo¨gren syndrome; 10 right eyes of 10 normal subjects served as the control. Serial measurements of VAs using a functional VA measurement system and higher order aberrations using a wavefront sensor were performed under blink-free conditions without topical anesthesia over a 10-second period. The parameters for each measurement were compared among the SPK-positive and -negative and normal groups. The correlation between those parameters was also analyzed.

RESULTS. Dry eye with SPK showed significant deterioration of visual function and optical quality compared with dry eye without SPK and in normal eyes, as detected by both the visual maintenance ratio (VMR: P < 0.05) and the variation of VA (P < 0.05) and by comalike and total higher order aberrations (P < 0.05). Moreover, the severity of epithelial damage at the central cornea correlated significantly with VMR (P < 0.01) and variation of VA (P < 0.01) as well as comalike (P < 0.05) and total higher order aberrations (P < 0.05). The dry eye group without SPK showed minor visual deterioration compared with normal eyes, as detected only by VMR (P < 0.05).

CONCLUSIONS. Optical disturbances at the central optical zone of the cornea in dry eye disease may affect visual performance. Functional VA measurement may be an applicable method of evaluating visual performance in dry eye patients that is as efficient as wavefront aberration measurements. (Invest Ophthalmol Vis Sci. 2011;52:9516–9522) DOI:10.1167/iovs.11-8412

Dynamic changes in the tear film have been the focus as the cause of visual deterioration. The tear film over the ocular surface forms the most superficial optical surface during blinking. When the tear film is normal, a smooth optical surface is formed over the cornea. On the other hand, when the tear film breaks up, the optical surface becomes irregular. Montes-Mico et al.21 reported the temporal changes in the higher order aberrations associated with the tear film surface in patients with dry eye by measuring the wavefront aberrations at 1-second time intervals for 15 seconds after a blink. Koh et al.22 focused on the superficial punctate keratopathy (SPK) associated with dry eye and investigated the main causes of optical quality deterioration, including SPK and the tear film changes by using the serial measurements of corneal higher order aberrations. They concluded that the SPK above the entrance pupil affects optical quality, but tear film changes corresponding to blinks do not affect the sequential increase in higher order aberrations after blinking. The deterioration of optical quality detected by the objective wavefront aberration method should be further investigated for a clearer understanding of the visual function of dry eye patients and their subjective complaints.

There are many subjective visual function assessment methods. Contrast sensitivity is considered an accurate method of measuring the quality of vision in patients with dry eye syndrome. It has been reported that contrast sensitivity is decreased in dry eye patients with the impaired ability to appreciate subtle differences in color or shape under low light or indirect bright-light conditions. Glare test may be also a useful method of reflecting visual disability. It was reported that irregularity of the ocular surface contributes to glare disability in the early phase of dry eye disease such as in dry eyes without SPK. Functional visual acuity (VA), which evaluates the time-wise changes in VA, can also be a helpful method of detecting the masked impairment of visual performance in dry eye patients who report decreased VA despite showing normal VA in standard VA testing.

However, little is known about the relation between the objective and quantitative assessment of optical and subjective quality of vision in dry eye patients. We selected wavefront aberration and functional VA for use in investigating the major causes of visual deterioration in dry eye patients with Sjögren syndrome, and investigated whether SPK or tear film change causes the major visual deterioration. We also investigated the correlation between serial ocular wavefront aberrations and functional VA.

METHODS

Patients

Twenty-two right eyes of 22 dry eye patients with Sjögren syndrome (1 male, 21 females; mean age, 57.4 ± 14.8 years; range, 34–87) and 10 right eyes of 10 healthy volunteers (5 males, 5 females; mean age, 47.8 ± 6.8 years; range, 41–61) seen at the dry eye subspecialty outpatient clinic of...
the Department of Ophthalmology at Keio University were enrolled in this study. Sjögren syndrome was diagnosed according to the Fox criteria. Exclusion criteria included a history of ocular trauma, abnormality of the nasolacrimal drainage apparatus, permanent occlusion of lacrimal puncta, temporary punctal plug occlusion, and contact lens wearing. This research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after explanation of the nature and possible consequences of the study.

**Tear Function Evaluation**

The Schirmer test was performed without topical anesthesia. Standardized strips of filter paper (Showa Yakuhin, Tokyo, Japan) were placed in the lateral canthus away from the cornea and left in place for 5 minutes with the eyes closed. Readings were reported in millimeters of wetting for 5 minutes.

The standard tear film break-up time (BUT) measurement was performed after instillation of a 2-μL volume of a preservative-free solution of 1% fluorescein in the conjunctival sac with a micropipette. The patient was then instructed to blink several times for a few seconds to ensure adequate mixing of the dye. The interval between the last complete blink and the appearance of the first corneal black spot in the stained tear film was measured three times, and the mean value of the measurements was calculated. BUT ≤ 5 seconds was considered abnormal. A cobalt blue filter was used to measure the BUT.

Scoring of the ocular surface was performed with 1% fluorescein dye and 1% rose bengal stain. The rose bengal and fluorescein staining scores of the ocular surface ranged between 0 and 9 points. The van Bijsterveld scoring system, in which the ocular surface was divided into three zones—nasal conjunctival, corneal, and temporal conjunctival—was used. In each zone, a staining score in points was used, with the minimum being 0 and the maximum 3.

**The Functional Visual Acuity Measurement System**

The Functional VA Measurement System (Nidek, Gamagori, Japan) was used to examine the time-wise change in continuous VA. The device comprises three parts: a hard disc, a monitor, and a joystick. The Landolt optotypes are presented on the monitor, and their sizes change, depending on the correctness of the responses. In brief, the optotypes are displayed automatically starting with the smaller ones. When the response is correct, smaller optotypes are presented. If the responses are incorrect, larger optotypes are presented automatically. Visual acuity is continuously measured from the baseline Landolt VA, which is the best corrected Landolt VA. The Functional VA Measurement System can measure VA from 20/10 to 20/200, depending on the choice of examination distance (1, 2.5, or 5 m). The monitor was placed at 5 m from the subjects in the present study. When there was no response within the set display times, the answer was assumed to be an error, and the optotype was automatically enlarged.

The outcomes were denoted as starting VA, logMAR functional VA, visual maintenance ratio (VMR), and variation in VA. Starting VA was defined as the baseline, which was the standard best corrected VA measured by the functional VA measurement system. Functional VA was defined as the mean time-wise change in VA during the overall examination, not the value at one point during the examination. The VMR was the ratio of functional VA divided by the baseline. In brief, the VMR was calculated as: VMR = (lowest logMAR VA score − functional VA at 10 seconds)/(lowest logMAR VA score − baseline VA). The variation of VA was defined as the value obtained by subtracting the logMAR maximum VA score from the logMAR minimum VA score during the 10-second measurement period.

Functional VA was measured during a 10-second period without the instillation of topical anesthesia. Subjects were instructed to keep their eyelids open during the measurement period. Patients indicated the orientation of the automatically presented Landolt rings by manipulating the joystick. Functional VA testing was performed after tear function testing.

**Sequential Measurement of Wavefront Aberrations**

Serial measurements of ocular higher order aberrations were performed by using the Hartmann-Shack wavefront aberrometer (Topcon Corp., Tokyo, Japan). Higher-order aberrations were measured during a blink-free 10-second period under the same conditions as the functional VA measurement, without the instillation of topical anesthesia. The higher order aberration data were analyzed quantitatively in the central 4-mm diameter up to the fourth order by expanding the set of Zernike polynomials. From the Zernike coefficients, the root mean square (RMS) was calculated to represent the wavefront aberrations. S3 and S4 are the RMS of the third- and fourth-order Zernike coefficients, respectively. Comalike aberrations (S3), spherical-like aberrations (S4), and total higher order aberrations (S3+S4) were also calculated.

Two quantitative indexes were used to indicate the sequential change in higher order aberrations over a 10-second measurement period: the fluctuation index and the stability index of the total higher order aberrations. The fluctuation index was defined as the average of the standard deviation of the ocular total higher order aberrations, and stability index was defined as the slope of the linear regression line of the total ocular higher order aberrations measured during a 10-second period with blink suppression.

**Statistical Analysis**

A repeated-measures one-way ANOVA was used to analyze the relation among the groups with or without SPK and in the normal group in relation to the functional VA and higher order aberration parameters. The Tukey test was used for further multiple comparisons of the functional VA and higher order aberration parameters between the groups. The correlations between the functional VA or wavefront aberration parameters and the severity of epithelial damage at the center of the cornea were analyzed by Pearson’s correlation analysis. The severity of epithelial damage at the central zone in the cornea was divided into three degrees: no staining, mild staining, and severe staining of fluorescein (Fig. 1). The correlation between the functional VA and wavefront aberration parameters was also analyzed by Pearson’s correlation analysis.
son’s correlation analysis (SPSS software version 12.0J for Windows; SPSS Inc., Chicago, IL). \( P < 0.05 \) was considered statistically significant.

**RESULTS**

**Tear Function Assessments**

The profile of the tear functions and vital staining scores of the groups, with or without SPK, and the normal control group are shown in Table 1.

**Functional Visual Acuity Parameters**

The mean starting VA scores of the group, with or without SPK, and the control group were \(-0.02 \pm 0.12, -0.07 \pm 0.07, \) and \(0.02 \pm 0.03\), respectively. No significant differences were observed in the starting VA in each group \((P > 0.05)\). Figure 2 shows the mean functional VA score, the VMR, and the variation of VA values in each group. The mean functional VA scores in the groups with or without SPK and in the normal group were \(0.12 \pm 0.14, 0.02 \pm 0.09, \) and \(0.02 \pm 0.06\), respectively. The logMAR functional VA scores in the group with SPK tended to be higher than in the group without \((P = 0.08)\) and the normal group \((P = 0.07)\) without statistical significance. The mean VMR values in the groups with or without SPK and in the normal group were \(0.95 \pm 0.02, 0.97 \pm 0.01, \) and \(1.0 \pm 0.02\), respectively, whereas the mean variations in VA were \(0.25 \pm 0.08, 0.15 \pm 0.04, \) and \(0.13 \pm 0.06\), respectively. The VMR values in the group with SPK were significantly lower than those in the group without and the normal group \((P < 0.05)\). In addition, the VMR values in the group without SPK were significantly larger than in the group without and the normal group \((P < 0.05)\).

Table 2A shows the correlations between the wavefront aberration parameters and the severity of epithelial damage at the center of the cornea. The VMR value showed a strong negative correlation, whereas a variation in VA showed a strong positive correlation with the severity of epithelial damage at the center of cornea \((P < 0.01)\).

**Ocular Higher Order Aberration Parameters**

Figure 3 shows the mean comalike aberration, spherical aberration, total higher order aberrations, the fluctuation index, and the stability index in each group. The mean comalike aberrations in the groups with or without SPK and in the normal group were \(0.190 \pm 0.086, 0.149 \pm 0.060, \) and \(0.100 \pm 0.031\), respectively. The mean spherical aberrations in each group were \(0.100 \pm 0.050, 0.092 \pm 0.049, \) and \(0.082 \pm 0.027\), respectively. The mean total higher order aberrations in each group were \(0.220 \pm 0.093, 0.178 \pm 0.074, \) and \(0.132 \pm 0.041\), respectively. The comalike and total higher order aberrations in the group with SPK were significantly higher than those in the group without SPK and in the normal group \((P < 0.05)\), whereas there were no significant differences in the spherical-like aberrations among the three groups.

The mean fluctuation indexes in each group were \(0.042 \pm 0.056, 0.033 \pm 0.032, \) and \(0.017 \pm 0.013\), respectively. The mean stability indexes in each group were \(0.013 \pm 0.035, -0.004 \pm 0.029, \) and \(0.000 \pm 0.002\), respectively. There were no significant differences in the fluctuation indexes and stability indexes between the three groups.

Table 2B shows the correlations between the wavefront aberration parameters and the severity of epithelial damage at the center of the cornea. The comalike aberrations showed a strong positive correlation and the total higher order aberrations showed a strong negative correlation with the severity of epithelial damage at the center of the cornea \((P < 0.05)\).

**Serial Changes in Higher Order Aberrations**

Figure 4 shows the averages of the sequential changes in higher order aberrations during the measurements in each group. In all groups, significant changes were not observed at

<table>
<thead>
<tr>
<th>Schirmer Value (mm)</th>
<th>Fluorescein Score (Points)</th>
<th>Rose Bengal Score (Points)</th>
<th>BUT (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPK(+) group, ( n = 10 )</td>
<td>(2.9 \pm 0.2^*)</td>
<td>(4.5 \pm 2.4^*)</td>
<td>(4.5 \pm 2.4^*)</td>
</tr>
<tr>
<td>SPK(−) group, ( n = 12 )</td>
<td>(3.3 \pm 2.8^*)</td>
<td>(1.2 \pm 0.9)</td>
<td>(1.2 \pm 0.9)</td>
</tr>
<tr>
<td>Normal group, ( n = 10 )</td>
<td>(9.5 \pm 4.3)</td>
<td>(0.1 \pm 0.3)</td>
<td>(0.1 \pm 0.3)</td>
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\(^* P < 0.05\) between groups of dry eyes and normal eyes.
was detected by both VMR and variation in VA, and comalike
pared with dry eye without SPK and in the normal eyes, which
dry eye with SPK showed significant visual deterioration com-
tutional VA and wavefront aberration parameters. We found that
rometer, and also looked into the correlation between func-
system, investigated optical quality with the wavefront aber-
visual performance when measured with the functional VA
corneal surface with an unstable, thin tear film would affect
We conducted the present study to assess how an irregular
DISCUSSION
ever point over 10 seconds in the sequential comalike, spher-
cal-like, and total higher order aberrations. Only in the group
with SPK did the sequential total higher order and comalike aberrations tend to fluctuate during the measurement period.

Correlation between Functional Visual Acuity and Wavefront Aberration Parameters
The correlations between functional VA and wavefront param-
eters were analyzed as shown in Table 3. VMR showed signif-
ificant negative correlation with comalike and total higher order aberrations ($P < 0.05$). The variation in VA also correlated significantly with stability indexes.

DIsCUSSION
We conducted the present study to assess how an irregular corneal surface with an unstable, thin tear film would affect visual performance when measured with the functional VA system, investigated optical quality with the wavefront aber-
rometer, and also looked into the correlation between func-
tional VA and wavefront aberration parameters. We found that dry eye with SPK showed significant visual deterioration compared with dry eye without SPK and in the normal eyes, which was detected by both VMR and variation in VA, and comalike and total aberrations. Moreover, the severity of epithelial dam-
age at the central cornea correlated significantly with VMR and variation in VA, as well as comalike and total aberrations. These findings showed that when the severity of corneal epithelial damage at the central corneal zone was greater, there was a greater degree of visual performance deterioration. According to the correlation coefficients, the functional VA parameters may very well reflect the effect of the severity of the epithelial damage on visual function as efficiently as the wavefront aberration parameters.

Concerning the comparisons between dry eyes without SPK and normal eyes, only VMR, one of the FVA parameters, showed a significant difference. The result of the difference in VMR between the normal and dry eyes without staining seems to reflect the effect of an unstable tear film on visual acuity in the absence of clinically apparent surface cell damage. Dry eye with no staining or very little staining may lie in the dry eye category of short BUT, which is characterized by significant symptomatology due to irritation of the sensory nerve endings in the absence of staining of the ocular surface. Indeed, Bourcier et al. reported that alternations in the thickness and composition of the tear film would enhance the mechanical stimuli from blinks to the corneal nerve endings, causing increased symptoms. In a previous study, we suggested that functional VA was decreased in short-BUT dry eye, and functional VA was improved after punctal plug insertion. We found outcomes similar to those that we found in a previous study. In that study, we reported that functional VA correlated significantly with not only the ocular surface vital staining scores but also with tear stability. A positive correlation be-
tween tear stability and functional VA suggests poor visual performance in short-BUT dry eye with no or minimal epithelial damage. Optical irregularities from dryness may indeed result in a reduction of optical quality. It is also possible that the loss of a stable tear film between the blinks would be the likely cause of the greater effect on vision, whereas the inher-
ent instability of the tear film alone could account for the effect on functional vision noted in those without central staining. Since the tear film stability is impaired and the tear evaporation rate has been reported to increase in short-BUT dry eye, future studies investigating the effect of tear evaporation and tear retention volume (by OCT or other imaging techniques) on visual acuity and wavefront parameters in evaporative dry eye patients will provide very useful information. Previous studies

<table>
<thead>
<tr>
<th>Severity of epithelial damage</th>
<th>Starting VA Pearson CC</th>
<th>$P$</th>
<th>Functional VA Pearson CC</th>
<th>$P$</th>
<th>VMR Pearson CC</th>
<th>$P$</th>
<th>Variation of VA Pearson CC</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.049</td>
<td>0.791</td>
<td>0.286</td>
<td>0.113</td>
<td>-0.513*</td>
<td>0.003</td>
<td>0.555*</td>
<td>0.001</td>
</tr>
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**B. Higher-Order Aberrations versus Damage Severity**

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</tr>
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<tbody>
<tr>
<td></td>
<td>0.426†</td>
<td>0.015</td>
<td>0.134</td>
<td>0.465</td>
<td>-0.382†</td>
<td>0.034</td>
<td>0.269</td>
<td>0.137</td>
<td>0.307</td>
</tr>
</tbody>
</table>

CC. Correlation coefficient; VA. visual acuity; VMR. visual maintenance ratio.
* $P < 0.01$.
† $P < 0.05$.

![Figure 3](image_url)

**Figure 3.** The comparison of the wavefront aberrations parameters in each group. Comalike and total higher order aberrations in the group with SPK were significantly higher than those in the group without SPK and in the normal group ($P < 0.05$).
reported that visual performance was affected by the dynamics of tear film in dry eye patients compared to normal subjects.\textsuperscript{11,28,36} However, detailed information of epithelial damage relating to the extent of area involvement in the cornea has not been described before. Koh et al.\textsuperscript{22} have assessed visual performance in dry eye without SPK by wavefront aberrometer. They did not detect differences between dry eyes without SPK and normal eyes. On the other hand, we detected a significant difference between dry eye without SPK and normal eyes using the functional VA measurement system, which suggested that the dynamics of tear film without structural corneal changes can also cause visual functional disturbance. The functional VA system may be a more sensitive tool for detecting the minimal differences in visual performance related to tear film dynamics.

When we looked at the serial changes in total higher order aberrations, we did not obtain any significant differences in the specific patterns, with or without dry eyes. Montes-Mico et al.\textsuperscript{21} reported the temporal changes in the higher order aberrations associated with the tear film surface in patients with dry eye, by measuring the wavefront aberrations at 1-second intervals for 15 seconds after a blink. Similar to their findings, other reports also showed, by the continuous measurement of wavefront aberration, that higher order aberrations tend to increase sequentially in dry eyes.\textsuperscript{21} On the other hand, Koh et al.\textsuperscript{22} showed the presence of fluctuations in higher order aberrations, similar to the outcomes obtained from this study. We agree with the assumption that SPK plays the dominant role in visual performance, but tear stability may not affect ocular higher order aberrations so much as corneal epithelial damage. Although the tear film stability is considerably impaired and tear evaporation rate is increased in dry eye, the decreased volume of tear film may be insufficient to cause the dynamic upward curve in higher order aberrations, or the dynamic upward curve may be observed before the tear film break-up. Koh et al. suggested that a certain amount of tear film thickness may be a main factor in the development of the dynamic change in higher order aberrations. The absence of a marked upward curve in dry eye may result from the thin

![Figure 4](https://example.com/f4.png)

**Figure 4.** The sequential changes in higher order aberrations over 10 seconds. Significant changes were not observed at every point over 10 seconds in the sequential coma-like, spherical-like, and total higher order aberrations in each group. Errors bars have been omitted for clarity.

### Table 3. Correlations between Functional Visual Acuity and Higher Order Aberrations

<table>
<thead>
<tr>
<th></th>
<th>Coma-like Aberration</th>
<th>Spherical-like Aberration</th>
<th>Total Higher-Order Aberration</th>
<th>Fluctuation Index</th>
<th>Stability Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting VA</td>
<td>−0.012</td>
<td>0.015</td>
<td>0.181</td>
<td>0.323</td>
<td>0.035</td>
</tr>
<tr>
<td>Functional VA</td>
<td>0.305</td>
<td>0.089</td>
<td>0.341</td>
<td>0.056</td>
<td>0.331</td>
</tr>
<tr>
<td>VMR</td>
<td>−0.505*</td>
<td>0.005</td>
<td>−0.307</td>
<td>0.088</td>
<td>−0.485*</td>
</tr>
<tr>
<td>Variation of VA</td>
<td>0.356</td>
<td>0.060</td>
<td>0.065</td>
<td>0.722</td>
<td>0.281</td>
</tr>
</tbody>
</table>

* $P < 0.01$.
† $P < 0.05$. 

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aqueous tear film layer, because tear film breaks up rapidly in dry eye and the decrease in tear film thickness may persist. In cases of milder dry eyes, which may cause reflex tearing, a sequential upward curve in higher order aberrations may be observed.

We observed that there were three types of patterns of sequential VAs in functional VA; a steep downward pattern, a small-fluctuation pattern, and an intermediate type between the two former patterns. The variation of VA changes in dry eyes with SPK was large, although sequential higher order aberrations in these eyes showed stable changes. This variation in VA data seems not to correspond with the dynamic changes in higher order aberrations. This finding may suggest that the functional VA measurement more faithfully reflects the condition of the ocular surface with SPK and is able to detect even minimal visual deterioration in dry eyes, even when the tear film is thin and insufficient. We have reported in a previous study that functional VA correlated with not only Schirmer values and vital staining scores, but also tear stability. It is known that functional VA in normal eyes is not decreased and that the sequential VAs remain stable. On the other hand, in our experience, VAs in the aqueous-deficient type of dry eye due to Sjögren syndrome declined and did not recover to baseline levels, whereas sequential VAs in short-BUT dry eye without corneal damage mostly fluctuated during the functional VA measurement period.

Interestingly, we observed correlations between VMR and corneal or total higher order aberrations (P < 0.01) and between the variation in VA and the stability index (P < 0.05). This is an important observation that suggests that VMR may reflect the optical vision quality similar to measurements attained by wavefront aberrometer.

In conclusion, epithelial damage at the central optical zone of the cornea appears to be an important factor in impaired visual performance. Functional VA measurement may be an applicable method for evaluating the visual performance in dry eyes as efficiently as wavefront aberration measurements, which can objectively evaluate optical vision quality. Further studies investigating the relation of dynamic assessment of tear film break-up with outcome of functional VA and wavefront aberrations should be performed.

References


